(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 816 837 A1

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
07.01.1998 Bulletin 1998/02

(51) Int Cl.6: G01N 27/447

(21) Application number: 97304873.9

(22) Date of filing: 03.07.1997

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV RO SI

(30) Priority: 03.07.1996 US 678436

(71) Applicant: Caliper Technologies Corporation
Palo Alto, California 94304 (US)

(72) Inventors:
- Chow, Calvin Y.H.
Porta Valley, CA 94028 (US)
- Parce, J Wallace
Palo Alto, CA 94304 (US)

(74) Representative: Williamson, Brian et al
Hepworth Lawrence Bryer & Bizley
Merlin House
Falconry Court
Baker's Lane
Epping Essex CM16 5DQ (GB)

(54) **Variable control of electroosmotic and/or electrophoretic forces within a fluid-containing structure via electrical forces**

(57) In a microfluidic system using electrokinetic forces, the present invention uses electrical current or electrical parameters, other than voltage, to control the movement of fluids through the channels of the system. Time-multiplexed power supplies also provide further control over fluid movement by varying the voltage on an electrode connected to a fluid reservoir of the microfluidic system, by varying the duty cycle during which the voltage is applied to the electrode, or by a combination of both. A time-multiplexed power supply can also be connected to more than one electrode for a savings in cost.

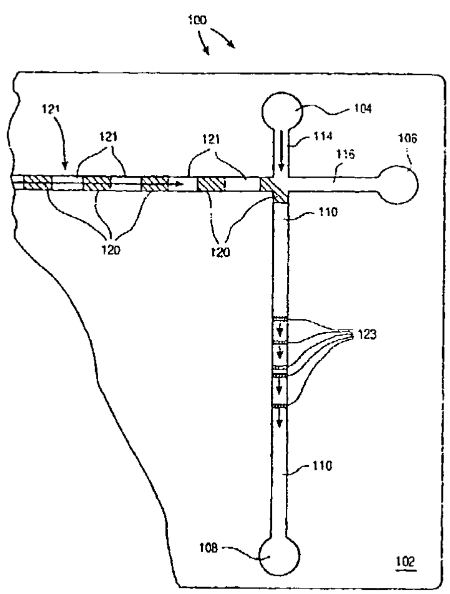

FIG. 1

EP 0 816 837 A1

Description

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application Serial No. 08/678,436, filed July 3, 1996, which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

There has been a growing interest in the manufacture and use of microfluidic systems for the acquisition of chemical and biochemical information. Techniques commonly associated with the semiconductor electronics industry, such as photolithography, wet chemical etching, etc., are being used in the fabrication of these microfluidic systems. The term, "microfluidic", refers to a system or device having channels and chambers which are generally fabricated at the micron or submicron scale, e.g., having at least one cross-sectional dimension in the range of from about 0.1 μm to about 500 μm. Early discussions of the use of planar chip technology for the fabrication of microfluidic systems are provided in Manz et al., Trends in Anal. Chem. (1990) 10 (5):144-149 and Manz et al., Avd. in Chromatog. (1993) 33:1-66, which describe the fabrication of such fluidic devices and particularly microcapillary devices, in silicon and glass substrates.

Applications of microfluidic systems are myriad. For example, International Patent Appln. wO 96/04547, published February 15, 1996, describes the use of microfluidic systems for capillary electrophoresis, liquid chromotography, flow injection analysis, and chemical reaction and synthesis. A related patent application, U. S. Appln. No._____, entitled "HIGH THROUGHPUT SCREENING ASSAY SYSTEMS IN MICROSCALE FLUIDIC DEVICES", filed June 28, 1996 by J. Wallace Parce et al. and assigned to the present assignee, discloses wide ranging applications of microfluidic systems in rapidly assaying compounds for their effects on various chemical, and preferably, biochemical systems. The phrase, "biochemical system" generally refers to a chemical interaction that involves molecules of the type generally found within living organisms. Such interactions include the full range of catabolic and anabolic reactions which occur in living systems including enzymatic, binding, signaling and other reactions. Biochemical systems of particular interest include, e.g., receptor-ligand interactions, enzyme-substrate interactions, cellular signaling pathways, transport reactions involving model barrier systems (e.g., cells or membrane fractions) for bioavailability screening, and a variety of other general systems.

Many methods have been described for the transport and direction of fluids, e.g., samples, analytes, buffers and reagents, within these microfluidic systems or devices. One method moves fluids within microfabricated devices by mechanical micropumps and valves within the device. See, Published U.K. Patent Application No. 2 248 891 (10/18/90), Published European Patent Application No. 568 902 (5/2/92), U.S. Patent Nos. 5,271,724 (8/21/91) and 5.277,556 (7/3/91). See also, U.S. Patent No. 5,171,132 (12/21/90) to Miyazaki et al. Another method uses acoustic energy to move fluid samples within devices by the effects of acoustic streaming. See, Published PCT Application No. 94/05414 to Northrup and White. A straightforward method applies external pressure to move fluids within the device. See, e.g., the discussion in U.S. Patent No. 5,304,487 to Wilding et al.

Still another method uses electric fields, and the resulting electrokinetic forces, to move fluid materials through the channels of the microfluidic system. See, e. g., Published European Patent Application No. 376 611 (12/30/88) to Kovacs, Harrison et al., Anal. Chem. (1992) 64:1926-1932 and Manz et al. J. Chromatog. (1992) 593:253-258, U.S. Patent No. 5,126,022 to Soane. Electrokinetic forces have the advantages of direct control, fast response and simplicity. However, there are still some disadvantages with this method of operating a microfluidic system.

Present devices use a network of channels in a substrate of electrically insulating material. The channels connect a number of fluid reservoirs in contact with high voltage electrodes. To move fluid materials through the network of channels, specific voltages are simultaneously applied to the various electrodes. The determination of the voltage values for each electrode in a system becomes complex as one attempts to control the material flow in one channel without affecting the flow in another channel. For example, in a relatively simple arrangement of four channels intersecting in a cross with reservoirs and electrodes at the ends of the channels, an independent increase of fluid flow between two reservoirs is not merely a matter of increasing the voltage differences at the two reservoirs. The voltages at the other two reservoirs must also be adjusted if their original flow and direction are to be maintained. Furthermore, as the number of channels, intersections, and reservoirs are increased, the control of fluid through the channels become more and more complex.

Also, the voltages applied to the electrodes in the device can be high, i.e., up to a level supportive of thousands of volts/cm. Regulated high voltage supplies are expensive, bulky and are often imprecise and a high voltage supply is required for each electrode. Thus the cost of a microfluidic system of any complexity may become prohibitive.

The present invention solves or substantially mitigates these problems of electrokinetic transport in a microfluidic system which uses another electrical parameter, rather than voltage, to simplify the control of material flow through the channels of the system. A high throughput microfluidic system having direct, fast and straightforward control over the movement of materials

through the channels of the microfluidic system with a wide range of applications, such as in the fields of chemistry, biochemistry, biotechnology and molecular biology and numerous other fields, is possible.

SUMMARY OF THE INVENTION

The present invention provides for a microfluidic system with a plurality of interconnected capillary channels and a plurality of electrodes at different nodes of the capillary channels which create electric fields in the capillary channels to electrokinetically move materials in a fluid through the capillary channels. In accordance with the present invention, the microfluidic system is operated by applying a voltage between a first electrode and a second electrode responsive to an electrical current between the first and second electrodes to move materials therebetween. Electrical current can give a direct measure of ionic flow through the channels of the microfluidic system. Besides current, other electrical parameters, such as power, may be also used.

Furthermore, the present invention provides for time-multiplexing the power supply voltages on the electrodes of the microfluidic system for more precise and efficient control. The voltage to an electrode can be controlled by varying the duty cycle of the connection of the electrode to the power supply, varying the voltage to the electrode during the duty cycle, or a combination of both. In this manner, one power supply can service more than one electrode.

The present invention also provides for the direct monitoring of the voltages within the channels in the microfluidic system. Conducting leads on the surface of the microfluidic system have widths sufficiently narrow in a channel to prevent electrolysis. The leads are connected to voltage divider circuits also on the surface of the substrate. The divider circuit lowers the read-out voltage of the channel node so that special high-voltage voltmeters are not required. The divider circuits are also designed to draw negligible currents from the channels thereby minimizing unwanted electrochemical effects, e.g., gas generation, reduction/ oxidation reactions.

The invention as hereinbefore described may be put to a plurality of different uses, which are themselves inventive, for example, as follows:

The use of a substrate having at least one channel in which a subject material is transported electrokinetically, by applying a voltage between two electrodes associated with the channel in response to a current at the electrodes.

A use of the aforementioned invention, in which the substrate has a plurality of interconnected channels and associated electrodes, subject material being transported along predetermined paths incorporating one or more of the channels by the application of voltages to predetermined electrodes in response to a current at the electrodes.

The use of a substrate having at least one channel in which a subject material is transported electrokinetically by the controlled time dependent application of an electrical parameter between electrodes associated with the channel.

A use of the aforementioned invention, wherein the electrical parameter comprises voltage, current or power.

The use of an insulating substrate having a plurality of channels and a plurality of electrodes associated with the channels, the application of voltages to the electrodes causing electric fields in the channels, and at least one conductive lead on the substrate extending to a channel location so that an electric parameter at the channel location can be determined.

A use of the aforementioned invention, wherein the conductive lead has a sufficiently small width such that a voltage of less than 1 volt, and preferably less than 0.1 volt, is created across the conductive lead at the channel location.

A use of an insulating substrate having a plurality of interconnected capillary channels, a plurality of electrodes at different nodes of the capillary channels for creating electric fields in the capillary channels to move materials electrokinetically in a fluid through the capillary channels, a power supply connected to at least one of the electrodes, the power supply having a mixing block having a first input terminal for receiving a controllable reference voltage and a second input terminal, and an output terminal; a voltage amplifier connected to the mixing block output terminal, the voltage amplifier having first and second output terminals, the first output terminal connected to the at least one electrode; and a feedback block connected to the first output terminal of the voltage amplifier, the feedback block having an output terminal connected to the second input terminal of the mixing block so that negative feedback is provided to stabilize the power supply.

The use of the aforementioned invention, in which the feedback block is also connected to the second output terminal of the voltage amplifier, the feedback block generating a first feedback voltage responsive to a voltage at the first output terminal and a second feedback voltage responsive to an amount of current being delivered to the at least one electrode through the first output terminal, the feedback block having a switch for passing the first or second feedback voltage to the mixing block responsive to a control signal so that the power supply is selectably stabilized by voltage or current feedback.

The use of a power supply for connection to at least one electrode of a microfluidic system in which the power supply has a mixing block having a first input terminal for receiving a controllable reference voltage and a second input terminal, and an output terminal; a voltage amplifier connected to the mixing block output terminal, the voltage amplifier having first and second output terminals, the first output terminal connected to the at least one electrode; and a feedback block connected to the first and second output terminals of the voltage amplifier

and to the second input terminal of the mixing block, the feedback block generating a first feedback voltage responsive to a voltage at the first output terminal and a second feedback voltage responsive to an amount of current being delivered to the at least one electrode through the first output terminal, the feedback block having a switch for passing the first or second feedback voltage to the mixing block responsive to a control signal so that the power supply is selectably stabilized in voltage or current by negative feedback.

The use of a microfluidic system in which a substrate has a plurality of interconnected capillary channels, a plurality of electrodes at different nodes of the capillary channels for creating electric fields in the capillary channels to move materials electrokinetically in a fluid through the capillary channels, and a plurality of power supplies connected to each one of the electrodes, each of the power supplies capable of selectively supplying a selected voltage and a selected amount of current as a source or sink to the connected electrodes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a representative illustration of a microfluidic system;

Figure 2A illustrates an exemplary channel of a microfluidic system, such as that of Figure 1; Figure 2B represents the electrical circuit created along the channel in Figure 2A;

Figure 3A is a graph of output voltage versus time for a prior art power supply; Figure 3B is a graph of output voltage versus time for a time-multiplexed power supply according to the present invention;

Figure 4A is a representative illustration of a microfluidic system operating with time-multiplexed voltages according to the present invention; Figure 4B is a block diagram illustrating the units of a power supply in Figure 4A;

Figure 5A is a representative illustration of a microfluidic system with voltage-monitored nodes according to the present invention; Figure 5B details the voltage divider circuit of Figure 5A; and

Figure 6A is a block diagram of the power supply unit of Figure 4B; Figure 6B is an amplifier block representation of the DC-DC converter block of Figure 6A.

DETAILED DESCRIPTION OF THE INVENTION

Figure 1 discloses a representative diagram of a portion of an exemplary microfluidic system 100 operating according to the present invention. As shown, the overall system 100 is fabricated in a planar substrate 102. Suitable substrate materials are generally selected based upon their compatibility with the conditions present in the particular operation to be performed by the device. Such conditions can include extremes of pH, temperature, ionic concentration, and application of electrical fields. Additionally, substrate materials are also selected for their inertness to critical components of an analysis or synthesis to be carried out by the system.

The system shown in Figure 1 includes a series of channels 110, 112, 114 and 116 fabricated into the surface of the substrate 102. As discussed in the definition of "microfluidic," these channels typically have very small cross sectional dimensions. For the particular applications discussed below, channels with depths of about 10 μm and widths of about 60 μm work effectively, though deviations from these dimensions are also possible. The microfluidic system 100 transports subject materials through the various channels of the substrate 102 for various purposes, including analysis, testing, mixing with other materials, assaying and combinations of these operations. The term, "subject materials," simply refers to the material, such as a chemical or biological compound, of interest. Subject compounds may include a wide variety of different compounds, including chemical compounds, mixtures of chemical compounds, e.g., polysaccharides, small organic or inorganic molecules, biological macromolecules, e.g., peptides, proteins, nucleic acids, or extracts made from biological materials, such as bacteria, plants, fungi, or animal cells or tissues, naturally occurring or synthetic compositions.

Useful substrate materials include, e.g., glass, quartz, ceramics and silicon, as well as polymeric substrates, e.g., plastics. In the case of conductive or semiconductive substrates, there should be an insulating layer on the substrate. This is important since the system uses electroosmotic forces to move materials about the system, as discussed below. In the case of polymeric substrates, the substrate materials may be rigid, semi-rigid, or non-rigid, opaque, semi-opaque or transparent, depending upon the use for which they are intended. For example, systems which include an optical or visual detection element, are generally be fabricated, at least in part, from transparent materials to allow, or at least, facilitate that detection. Alternatively, transparent windows of glass or quartz, e.g., may be incorporated into the device for these types detection elements. Additionally, the polymeric materials may have linear or branched backbones, and may be crosslinked or non-crosslinked. Examples of particularly preferred polymeric materials include, e.g., polydimethylsiloxanes (PDMS), polyurethane, polyvinylchloride (PVC) polystyrene, polysulfone, polycarbonate, polymethylmethacrylate (PMMA) and the like.

Manufacturing of these channels and other microscale elements into the surface of the substrate 102 may be carried out by any number of microfabrication techniques that are well known in the art. For example, lithographic techniques may be employed in fabricating glass, quartz or silicon substrates, for example, with methods well known in the semiconductor manufacturing industries. Photolithographic masking, plasma or wet etching and other semiconductor processing technologies define microscale elements in and on substrate

surfaces. Alternatively, micromachining methods, such as laser drilling, micromilling and the like, may be employed. Similarly, for polymeric substrates, well known manufacturing techniques may also be used. These techniques include injection molding techniques or stamp molding methods where large numbers of substrates may be produced using, e.g., rolling stamps to produce large sheets of microscale substrates or polymer microcasting techniques wherein the substrate is polymerized within a micromachined mold.

Besides the substrate 102, the microfluidic system 100 includes an additional planar element (not shown) which overlays the channeled substrate 102 to enclose and fluidly seal the various channels to form conduits. The planar cover element may be attached to the substrate by a variety of means, including, e.g., thermal bonding, adhesives or, in the case of certain substrates, e.g., glass, or semi-rigid and non-rigid polymeric substrates, a natural adhesion between the two components. The planar cover element may additionally be provided with access ports and/or reservoirs for introducing the various fluid elements needed for a particular screen.

The system 100 shown in Figure 1 also includes reservoirs 104, 106 and 108, which are disposed and fluidly connected at the ends of the channels 114, 116 and 110 respectively. As shown, the channel 112 is used to introduce a plurality of different subject materials into the device. As such, the channel 112 is fluidly connected to a source of large numbers of separate subject materials which are individually introduced into the channel 112 and subsequently into another channel 110 for electrophoretic analysis, for example. The subject materials are transported in fluid slug regions 120 of predetermined ionic concentrations. The regions are separated by buffer regions of varying ionic concentrations and represented by buffer regions 121 in Figure 1. Related patent applications, U.S. Appln. No. 08/671,986, filed June 28, 1996, and U.S. Appln. No. 08/760,446, filed December 6, 1996, both entitled "ELECTROPIPETTOR AND COMPENSATION MEANS FOR ELECTROPHORETIC BIAS," by J. Wallace Parce and Michael R. Knapp, and assigned to the present assignee, explain various arrangements of slugs, and buffer regions of high and low ionic concentrations in transporting subject materials with electrokinetic forces. The applications are incorporated herein by reference in their entirety for all purposes.

To move materials through the channels 110, 112, 114 and 116, a voltage controller which is capable of simultaneously applying selectable voltage levels, including ground, to each of the reservoirs, may be used. Such a voltage controller may be implemented using multiple voltage dividers and relays to obtain the selectable voltage levels. Alternatively, multiple independent voltage sources may be used. The voltage controller is electrically connected to each of the reservoirs via an electrode positioned or fabricated within each of the reservoirs 104, 106 and 108. See, for example, published International Patent Application No. WO 96/04547 to Ramsey, which is incorporated herein by reference in its entirety for all purposes.

Besides complexity, there are other problems with voltage control in a microfluidic system. Figure 2A illustrates an exemplary channel 130 between two reservoirs 132 and 134, each respectively in contact with electrodes 133 and 135, connected to electrical leads are shown leading off the substrate 128. To make the example more realistic, the channel 130 is shown as being connected to two other channels 136 and 138. Operationally, the reservoir 132 is a source for slugs 120 containing the subject material. The slugs 120 are moved toward the reservoir 134, which acts as a sink. The channels 136 and 138 provide buffer regions 121 to separate the slugs 120 in the channel 130.

The different resistances of the slugs 120 and buffer regions 121 in the channel 130 create an electrical circuit which is symbolically indicated in this simple example. The voltage V applied between the two electrodes 133 and 135 is:

$$V = I \sum_{i=0}^{n} R_i$$

where I is the current between the two electrodes 133, 135 (assuming no current flow into 136, 138) and R_i the resistance of the different slugs 120 and buffer regions 121.

A voltage control system is subject to many factors which can interfere with the operation of the system. For example, the contact at the interface between an electrode and fluid may be a source of problems. When the effective resistance of the electrode-to-fluid contact varies due to contaminants, bubbles, oxidation, for example, the voltage applied to the fluid varies. With V set at the electrodes, a decrease in electrode surface area contacting the solution due to bubble formation on the electrode causes an increase in resistance from the electrode to the solution. This reduces the current between electrodes, which in turn reduces the induced electroosmotic and electrophoretic forces in the channel 130.

Other problems may affect the channel current flow. Undesirable particulates may affect the channel resistance by effectively modifying the cross-sectional area of the channel. Again, with a change of channel resistance, the physical current flow is changed.

With other channels, such as channels 136 and 138, connected to the exemplary channel 130, dimensional variations in the geometry of the channels in the substrate 102 can seriously affect the operation of a voltage control system. For example, the intersection node for the channels 130, 136 and 138 might be X distance from the electrode for the reservoir at the terminus of

the channel 136 (not shown)and Y distance from the electrode for the reservoir at the terminus of the channel 138 (not shown). With a slight lateral misalignment in the photolithographic process, the distances X and Y are no longer the same for the microfluidic system on another substrate. The voltage control must be recalibrated from substrate to substrate, a time-consuming and expensive process, so that the fluid movement at the intersection node can be properly controlled.

To avoid these problems, the present invention uses electric current control in the microfluidic system 100. The electrical current flow at a given electrode is directly related to the ionic flow along the channel(s) connecting the reservoir in which the electrode is placed. This is in contrast to the requirement of determining voltages at various nodes along the channel in a voltage control system. Thus the voltages at the electrodes of the microfluidic system 100 are set responsive to the electric currents flowing through the various electrodes of the system 100. Current control is less susceptible to dimensional variations in the process of creating the microfluidic system on the substrate 102. Current control permits far easier operations for pumping, valving, dispensing, mixing and concentrating subject materials and buffer fluids in a complex microfluidic system. Current control is also preferred for moderating undesired temperature effects within the channels.

Of course, besides electric current which provides a direct measure of ionic flow between electrodes, other electrical parameters related to current, such as power, may be used as a control for the microfluidic system 100. Power gives an indirect measurement of the electric current through an electrode. Hence the physical current between electrodes (and the ionic flow) can be monitored by the power through the electrodes.

Even with a current control system described above, high voltages must still be applied to the electrodes of the microfluidic system. To eliminate the need for expensive power supplies which are capable of generating continuous and precise high voltages, the present invention provides for power supplies which are time-multiplexed. These time-multiplexed power supplies also reduce the number of power supplies required for the system 100, since more than one electrode can be serviced by a time-multiplexed power supply.

Figure 3A illustrates the exemplary output of a high power supply presently used in a electrokinetic system. The output is constant at 250 volts between two electrodes over time. In contrast, Figure 3B illustrates the output of a power supply operating according to the present invention. To maintain a constant voltage of 250 volts, the output voltage is time-multiplexed with a one-quarter duty cycle at 1000 volts. Averaged in time, the output of the time-multiplexed voltage supply is 250 volts, as illustrated by the horizontal dotted line across the graph. Note that if the voltage must change, say, in response to current control, as discussed above, the output voltage of the time-multiplexed power supply can also change by a change in the applied voltage, or by a change in the duty cycle, or a combination of both.

Electroosmotic fluid flow can be started and stopped on the μsecond time scale in channels of the dimensions described here. Therefore, voltage modulation frequencies which are lower than one Megahertz result in choppy movement of the fluids. This should have no adverse effects on fluid manipulation due to the plug flow nature of electroosmotic fluid. Because most chemical mixing, incubating and separating events occur on the 0.1 to 100 second time scale, the much lower frequencies for voltage manipulation may be acceptable. As a rule of thumb, the modulation period should be less than 1% of the shortest switching event (e.g., switching flow from one channel to another) to keep mixing or pipetting errors below 1%. For a switching event of 0.1 seconds, the voltage modulation frequency should be 1 KHz or higher.

Figure 4A is a block diagram of a multiplexed power supply system with two power supplies 200 and 202 and controller block 204 for an exemplary and simple microfluidic system having a channel 180 which intersects channels 182, 184, 186 and 188. The channel 180 terminates in reservoirs 179 and 181 with electrodes 190 and 191 respectively. The channel 182 ends with a reservoir 183 having an electrode 193; the channel 184 ends with a reservoir 185 having an electrode 195; the channel 186 with reservoir 187 having an electrode 197; and the channel 188 with reservoir 189 having an electrode 199.

The power supplies 200 and 202 are connected to the different electrodes 190, 191, 193, 195, 197 and 199 of the microfluidic system. The power supply 200 is connected to three electrodes 190, 193 and 195, and the power supply 202 is connected to the remaining three electrodes 191, 197 and 199. The controller block 204 is connected to each of the power supplies 200 and 202 to coordinate their operations. For instance, to control the movements of fluids through the channels 182, 184, 186 and 188, the voltages on the electrodes 190, 191, 193, 195, 197 and 199 must be properly timed. The voltages on the electrodes change in response to electric current flow, as described above, for example, as the controller block 204 directs the power supplies 200 and 202.

Each of the power supplies 200 and 202 are organized into units illustrated in Figure 4B. A control unit 212 receives control signals from the control block 204 and directs the operation of a switching unit 214. The switching unit 214, connected to a power supply unit 216, makes or breaks connections of the power supply unit 216 to the connected electrodes. In other words, the switching unit 214 time-multiplexes the power from the power supply unit 216 among its connected electrodes. The power supply unit 216 is also connected to the control unit 212 which directs the variation of output from the power supply unit 216 to the switching unit 214. In an alternate arrangement, this connection to the control

unit 212 is not required if the power supply unit 216 supplies a constant voltage and the averaged voltage to a electrode is changed by varying connection duty cycle through the switching unit 214.

Figure 6A is a block diagram of a power supply which could be used as the power supply unit 216 in Figure 4B. Alternatively, the illustrated power supply may be connected directly to an electrode of a microfluidic system if time-multiplexing is not used. The power supply can supply a stable voltage to an electrode or to supply, or sink, a stable current.

The power supply has an input terminal 240 which is supplied with a controllable reference voltage from -5 to +5 volts, which is stepped up in magnitude to hundreds of volts at an output terminal 241. The input terminal is connected to the negative input terminal of an input operational amplifier 230 through an resistance 227. The positive input terminal of an operational amplifier 230 is grounded and its output terminal is connected back to the negative input terminal through a feedback capacitor 220 and resistor 228 connected in series. The output terminal is also connected to an input terminal of a DC-to-DC converter 231. A second input terminal is grounded. The output side of the converter 231, which steps up the voltage received from the amplifier 230, is connected to the power supply output terminal 241. The second output terminal of the converter 231 is grounded through a resistor 222.

The power supply output terminal 241 is also connected to ground through two series-connected resistances 221 and 223 which form a voltage divider circuit. The node between the two resistances 221 and 223 is connected to one input terminal of a current/voltage mode switch 234. The node is also connected to the negative input terminal of a feedback operational amplifier 232 through a resistance 225. The negative input terminal is also connected to the output terminal of the converter 231 through a resistor 224 and to the output terminal of the amplifier 232 through a feedback resistor 226. The output terminal of the amplifier 232 is also connected to a second input terminal of the switch 234, which has its output terminal connected to the negative input terminal of the input operational amplifier 230 through a resistor 226.

The switch 234 is responsive to a signal on the control terminal 242. As shown in Figure 6A, the switch 234 connects its output terminal to either the output terminal of the feedback operational amplifier 232, or the voltage divider node between the two resistors 221 and 223. The connection determines whether the power supply circuit operates in the voltage mode (connection to the voltage divider node) or in the current mode (connection to the output of the feedback operational amplifier 232). Note that the resistor 221 is very large, approximately 15 MΩ, so that the voltage on the output terminal 241 can be easily fed back when the power supply is operated.

The Figure 6A circuit may be separated into different operational blocks. The operational amplifier 230, resistors 226-228 and capacitor 220 are part of a mixing block. The mixing block accepts the controllable reference voltage V_{ref}, about which the power supply operates, at the input terminal 240 and a feedback voltage, discussed below, to generate an output voltage, a combination of V_{ref} and feedback voltages, for the DC-DC converter 231. The converter 231, illustrated as a voltage amplifier in Figure 6B, simply amplifies the voltage from the operational amplifier 230. One output terminal of the voltage amplifier is connected to the output terminal 241 and a terminal of the resistor 221. The other output of the voltage amplifier is connected to ground through the resistor 222. The resistors 221-223 may be considered as part of a feedback block which also has resistors 224-226 and operational amplifier 232. The switch 234 is also part of the feedback block and is connected to the second input terminal of the mixing block, as described previously.

Operationally, the mixing block has the operational amplifier 230 which is connected as a summing amplifier with the resistances 226-228. With the capacitor 220 in the feedback loop of the operational amplifier 230, the output voltage of the operational amplifier 230 is the voltage integrated over time of the sum (or difference) of the reference voltage V_{ref} and the feedback voltage from the switch 234. Of course, the reference voltage V_{ref} and feedback voltage may be selectively weighted by the values of the resistances 226 and 227. The capacitor 220 and the amplifier 230 also act as a filter to remove high frequency fluctuations from the power supply.

The output signal from the operational amplifier 230 may be conditioned, for example, rectified or buffered, by additional elements (not shown). Nonetheless, for purposes of understanding this invention, V_{IN}, the voltage received by the DC-DC converter 231, can be considered the same as the output voltage of the operational amplifier 230. As shown in Figure 6B, V_{IN} is amplified by a gain factor A and the amplified voltage AV_{IN} is generated on the output terminal 241.

The feedback block has a voltage divider circuit formed by the resistors 221 and 223 connected between the output terminal 241 and ground. The voltage at the node between the resistors 221 and 223 is directly proportional to the voltage at the output terminal 241. When the switch 234 in response to the signal on the control terminal 242 selects the voltage feedback mode, the node voltage is fed directly back to the mixing block and the operational amplifier 230. The negative feedback stabilizes the output at the terminal 241. For example, if the voltage at the terminal 241 is high, the feedback voltage is high. This, in turn, causes the output voltage of the operational amplifier 230 to drop, thus correcting for the high voltage at the output terminal 241. For monitoring the voltage at the output terminal 241, the node is also connected to an operational amplifier 251, configured as a simple buffer, to send the feedback voltage to a monitoring circuit (not shown).

The feedback block also has the operational amplifier 232 and the resistances 224-226 which are connected to configure the operational amplifier 232 as a summing amplifier. One input to the summing amplifier is connected to the node between the resistors 221 and 223. The second input is connected to the node between the resistor 222 connected to ground and the second output terminal of the DC-DC converter 231. The summing amplifier measures the difference between the amount of current through the series-connected resistors 221 and 223 and through the converter 231 (the total current through the resistors 222 and 224). In effect, the summing amplifier measures the amount of current being delivered through the output terminal 241. Thus when the switch 234 is set in the current feedback mode, the output from the operational amplifier 232 acting as a summing amplifier is sent to the mixing block and the power supply circuit is stabilized about the amount of current being delivered through the power supply terminal 241 to a connected electrode of a microfluidic system.

The output of the summing amplifier is also connected to an operational amplifier 250, configured as a simple buffer, to send the output voltage to the monitoring circuit (not shown). From the outputs of the operational amplifiers 250 and 251, the monitoring circuit has a measure of the voltage at the output terminal 241 and of the current through the terminal. This also allows the monitoring circuit to determine, and to regulate, the amount of power being supplied by the power supply circuit.

The ability of the described power supply to act as a variable source allows the direction of fluid flow through the microchannels of a microfluidic system to be changed electronically. If all of the electrodes are connected to one or more of the power supplies described above, operation of the microfluidic system is greatly enhanced and the desired movements of fluids through the network of channels in the system are much more flexible.

Despite operation as a current control system, there is often still a need to determine the voltage at a node in a microfluidic system. The present invention also provides a means for such voltage monitoring. As shown in Figure 5A, an electrical lead 160 is formed on the surface of a substrate 178 near a desired node 173 in the microfluidic system. The node 173 is at the intersection of channel 170 having reservoirs 169 and 171 at each end and channels 172 and 174. The terminus of the channel 174 has a reservoir 175, while the terminus of the channel 172 (and a reservoir) is not shown.

The lead 160 is preferably formed by the deposition of a conductive metal, or metal alloy, preferably a noble metal, such as gold on chrome or platinum on titanium, used in integrated circuits. With semiconductor photolithography techniques, the lead 160 may be defined with widths of less than 1 μm. To prevent electrolysis, the width of the lead 160 in the channel 170 is narrow enough such that the voltage across the lead in the channel 170 should be less than 1 volt, preferably less 0.1 volt, at all times.

The voltages used in the microfluidic system are high. A voltmeter directly measuring the voltage at the channel node 173 through the lead 160 must have a very high input impedance to be capable of measuring such high voltages. Such voltmeters are expensive. Furthermore, handling of the substrate of the microfluidic systems increases the possibility of contamination. Such contamination can seriously affect the voltages (and electric fields) required for proper operation of electrokinetic forces in the channels of the microfluidic system.

To avoid these problems and costs, the lead 160 is connected to a voltage divider circuit 163, which is also formed on the surface of the substrate 178. The output of the voltage divider circuit 163 is carried by a conductive output lead 161. The circuit 163 is also connected by a conductive lead 162 to a voltage reference.

The voltage divider circuit 163, shown in greater detail in Figure 5B, is formed with standard semiconductor manufacturing technology with resistors 165 and 166 connected as a voltage divider circuit. The lead 160 is connected to the input terminal of the circuit 163, which is one end of a linear pattern of high-resistance material, such as undoped or lightly doped polysilicon or alumina. The other end of the linear pattern is connected to the reference lead 162, which is also formed on the substrate 168 and leads to an external reference voltage, presumably ground. As shown for explanatory purposes, the voltage of the lead 160 is divided in a 10-to-1 ratio. The linear pattern is divided into a resistor 165 and a resistor 166. The resistor 165 has nine times more loops than the resistor 166, i.e., the resistance of the resistor 165 is nine times greater than the resistance of the resistor 166. Of course, other ratios may be used and a 1000:1 ratio is typical. The output lead 161, connected between the two resistors 165 and 166, leads to an external connection for a low-voltage reading by a voltmeter. The cover plate then protects the leads 160-162, the voltage divider circuit 163 and the surface of the substrate from contamination.

While the foregoing invention has been described in some detail for purposes of clarity and understanding, it will be clear to one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention. All publications and patent documents cited in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication or patent document were so individually denoted.

Claims

1. In a microfluidic system having a plurality of inter-

connected capillary channels and a plurality of electrodes at different nodes of said capillary channels for creating electric fields in said capillary channels to electrokinetically move materials in a fluid through said capillary channels, a method of operating said microfluidic system comprising

applying voltages at said electrodes with respect to other electrodes in the system responsive to a current at said electrodes to move materials to and from channels of said electrodes.

2. The method of claim 1 wherein said microfluidic system has at least three electrodes.

3. The method of claim 2 wherein said voltage applying step comprises controlling said voltage so that said current is substantially constant.

4. In a microfluidic system having a plurality of capillary channels and a plurality of electrodes at different nodes of said capillary channels for creating electric fields in said capillary channels to electrokinetically move materials in a fluid through said capillary channels, a method of operating said microfluidic system comprising

controlling in time an application of an electrical parameter between electrodes in the system to move materials therebetween.

5. The method of claim 4 wherein said application is controlled such that said materials move equivalently to a constant application of said electrical parameters between said electrodes in the system.

6. The method of claim 5 wherein said application is controlled by varying a percentage of time said electrical parameter is applied.

7. The method of claim 4 wherein said electrical parameter comprises voltage.

8. The method of claim 4 wherein said electrical parameter comprises current.

9. The method of claim 4 wherein said electrical parameter comprises power.

10. A microfluidic system comprising

a plurality of capillary channels in an insulating substrate;
a plurality of electrodes at different nodes of said capillary channels for creating electric fields in said capillary channels to electrokinetically flow materials in a fluid through said capillary channels; and
at least one conductive lead on said substrate extending to a capillary channel location so that a voltage at said capillary channel location may be determined.

11. The microfluidic system of claim 10 wherein said conductive lead has a sufficiently small width such that a voltage of less than 1 volt is created across said conductive lead at said capillary channel location.

12. The microfluidic system of claim 11 wherein said conductive lead has a sufficiently small width such that a voltage of less than 0.1 volt is created across said conductive lead at said capillary channel location.

13. The microfluidic system of claim 10 wherein said conductive lead is arranged to form a voltage divider circuit on said substrate so that voltage received from said conductive lead is a fraction of said voltage at said capillary channel location.

14. The microfluidic system of claim 10 further comprising an insulating plate covering said substrate, said conductive lead extending to an edge of said substrate.

15. A microfluidic system comprising

a substrate having a plurality of interconnected capillary channels;
a plurality of electrodes at different nodes of said capillary channels for creating electric fields in said capillary channels to move materials electrokinetically in a fluid through said capillary channels;
a power supply connected to at least one of said electrodes, said power supply further comprising

a mixing block having a first input terminal for receiving a controllable reference voltage and a second input terminal, and an output terminal;
a voltage amplifier connected to said mixing block output terminal, said voltage amplifier having first and second output terminals, said first output terminal connected to said at least one electrode; and
a feedback block connected to said first output terminal of said voltage amplifier, said feedback block having an output terminal connected to said second input terminal of said mixing block so that negative feedback is provided to stabilize said power supply.

16. The microfluidic system of claim 15 wherein said feedback block is connected to said first output ter-

minal through a voltage divider circuit.

17. The microfluidic system of claim 16 wherein said feedback block provides feedback to said mixing block responsive to a voltage at said first output terminal.

18. The microfluidic system of claim 16 wherein said feedback block is connected to said second output terminal of said voltage amplifier so that said feedback block generates an output voltage responsive to an amount of current being sourced or sunk through said first output terminal, said feedback block providing feedback to said mixing block responsive to said current amount being sourced or sunk through said first output terminal.

19. The microfluidic system of claim 18 wherein said feedback block has a summing amplifier having a first input connected to said voltage divider circuit and a second input connected to said second output terminal of said voltage amplifier, said summing amplifier generating said output voltage responsive to said current amount being sourced or sunk through said first output terminal.

20. The microfluidic system of claim 16 wherein said feedback block is connected to said second output terminal of said voltage amplifier, said feedback block generating a first feedback voltage responsive to a voltage at said first output terminal and a second feedback voltage responsive to an amount of current being sourced or sunk through said first output terminal, said feedback block having a switch for passing said first or second feedback voltage to said mixing block responsive to a control signal so that the power supply is selectably stabilized by voltage or current feedback.

21. The microfluidic system of claim 20 further comprising first and second buffers connected to said feedback block, said first buffer transmitting said first feedback voltage and said second buffer transmitting said second feedback voltage so that said first and second feedback voltages may be monitored.

22. The microfluidic power supply of claim 15 wherein said mixing block comprises an operational amplifier connected as a summing amplifier.

23. The microfluidic power supply of claim 22 wherein said operational amplifier is further connected as an integrator.

24. A power supply for connection to at least one electrode of a microfluidic system comprising

a mixing block having a first input terminal for receiving a controllable reference voltage and a second input terminal, and an output terminal;
a voltage amplifier connected to said mixing block output terminal, said voltage amplifier having first and second output terminals, said first output terminal connected to said at least one electrode; and
a feedback block connected to said first and second output terminals of said voltage amplifier and to said second input terminal of said mixing block, said feedback block generating a first feedback voltage responsive to a voltage at said first output terminal and a second feedback voltage responsive to an amount of current being sourced or sunk through said first output terminal, said feedback block having a switch for passing said first or second feedback voltage to said mixing block responsive to a control signal so that the power supply is selectably stabilized in voltage or current by negative feedback.

25. The power supply of claim 24 wherein said feedback block is connected to said first output terminal of said voltage amplifier through a voltage divider circuit.

26. The power supply of claim 24 wherein said feedback block is connected to said second output terminal of said voltage amplifier so that said feedback block generates an output voltage responsive to an amount of current being sourced or sunk through said first output terminal.

27. The power supply of claim 24 further comprising first and second buffers connected to said feedback block, said first buffer transmitting said first feedback voltage and said second buffer transmitting said second feedback voltage so that said first and second feedback voltages may be monitored.

28. The power supply of claim 26 wherein said feedback block has a summing amplifier having a first input connected to said voltage divider circuit and a second input connected to said second output terminal of said voltage amplifier, said summing amplifier generating said output voltage responsive to said current amount being sourced or sunk through said first output terminal.

29. The power supply of claim 24 wherein said mixing block comprises an operational amplifier connected as a summing amplifier.

30. The power supply of claim 29 wherein said operational amplifier is further connected as an integrator.

31. A microfluidic system comprising

a substrate having a plurality of interconnected capillary channels;
a plurality of electrodes at different nodes of said capillary channels for creating electric fields in said capillary channels to move materials electrokinetically in a fluid through said capillary channels;
a plurality of power supplies connected to each one of said electrodes, each of said power supplies capable of selectively supplying a selected voltage or a selected amount of current as a source or sink to said connected electrodes.

32. The use of a substrate having at least one channel in which a subject material is transported electrokinetically, by applying a voltage between two electrodes associated with said channel in response to a current at said electrodes.

33. A use of claim 32 in which the substrate has a plurality of interconnected channels and associated electrodes, subject material being transported along predetermined paths incorporating one or more of said channels by the application of voltages to predetermined electrodes in response to a current at said electrodes.

34. The use of a substrate having at least one channel in which a subject material is transported electrokinetically by the controlled time dependent application of an electrical parameter between electrodes associated with said channel.

35. A use of claim 34 wherein said electrical parameter comprises voltage.

36. A use of claim 34 wherein said electrical parameter comprises current.

37. A use of claim 34 wherein said electrical parameter comprises power.

38. The use of an insulating substrate having a plurality of channels and a plurality of electrodes associated with said channels, the application of voltages to said electrodes causing electric fields in said channels, and at least one conductive lead on said substrate extending to a channel location so that an electric parameter at said channel location can be determined.

39. A use of claim 38 wherein said conductive lead has a sufficiently small width such that a voltage of less than 1 volt, and preferably less than 0.1 volt, is created across said conductive lead at said channel location.

40. The use of an insulating substrate having a plurality of interconnected capillary channels, a plurality of electrodes at different nodes of said capillary channels for creating electric fields in said capillary channels to move materials electrokinetically in a fluid through said capillary channels, a power supply connected to at least one of said electrodes, said power supply having a mixing block having a first input terminal for receiving a reference voltage and a second input terminal, and an output terminal; a voltage amplifier connected to said mixing block output terminal, said voltage amplifier having first and second output terminals, said first output terminal connected to said at least one electrode; and a feedback block connected to said first output terminal of said voltage amplifier, said feedback block having an output terminal connected to said second input terminal of said mixing block so that negative feedback is provided to stabilize said power supply.

41. The use of claim 40 in which said feedback block is also connected to said second output terminal of said voltage amplifier, said feedback block generating a first feedback voltage responsive to a voltage at said first output terminal and a second feedback voltage responsive to an amount of current being sourced or sunk through said first output terminal, said feedback block having a switch for passing said first or second feedback voltage to said mixing block responsive to a control signal so that said power supply is selectably stabilized by voltage or current feedback.

42. The use of a power supply for connection to at least one electrode of a microfluidic system in which said power supply has a mixing block having a first input terminal for receiving a reference voltage and a second input terminal, and an output terminal; a voltage amplifier connected to said mixing block output terminal, said voltage amplifier having first and second output terminals, said first output terminal connected to said at least one electrode; and a feedback block connected to said first and second output terminals of said voltage amplifier and to said second input terminal of said mixing block, said feedback block generating a first feedback voltage responsive to a voltage at said first output terminal and a second feedback voltage responsive to an amount of current being sourced or sunk through said first output terminal, said feedback block having a switch for passing said first or second feedback voltage to said mixing block responsive to a control signal so that said power supply is selectably stabilized in voltage or current by negative feedback.

43. The use of a microfluidic system in which a substrate has a plurality of interconnected capillary channels, a plurality of electrodes at different nodes of said capillary channels for creating electric fields

in said capillary channels to move materials electrokinetically in a fluid through said capillary channels, and a plurality of power supplies connected to each one of said electrodes, each of said power supplies capable of selectively supplying a selected voltage and a selected amount of current as a source or sink to said connected electrodes.

44. A microfluidic system comprising a substrate having at least one channel in which a subject material is transported electrokinetically, means for measuring electrical current and means for applying a voltage between two electrodes associated with said channel in response to said current at said electrodes.

45. A system as claimed in claim 44 in which the substrate has a plurality of interconnected channels and associated electrodes, subject material being transported along predetermined paths incorporating one or more of said channels by the application of voltages to predetermined electrodes in response to a current at said electrodes.

46. A microfluidic system comprising a substrate having at least one channel in which a subject material is transported electrokinetically, and means for the controlled time dependent application of an electrical parameter between electrodes associated with said channel.

47. A system as claimed in claim 46 wherein said electrical parameter comprises voltage.

48. A system as claimed in claim 46 wherein said electrical parameter comprises voltage.

49. A system as claimed in claim 46 wherein said electrical parameter comprises voltage.

50. A microfluidic system comprising an insulating substrate having a plurality of channels and a plurality of electrodes associated with said channels, and means for applying voltages to said electrodes in order to generate electric fields in said channels, and at least one conductive lead on said substrate extending to a channel location so that an electric parameter at said channel location can be determined.

51. A system as claimed in claim 50 wherein said conductive lead has a sufficiently small width such that a voltage of less than 1 volt, and preferably less than 0.1 volt, is created across said conductive lead at said channel location.

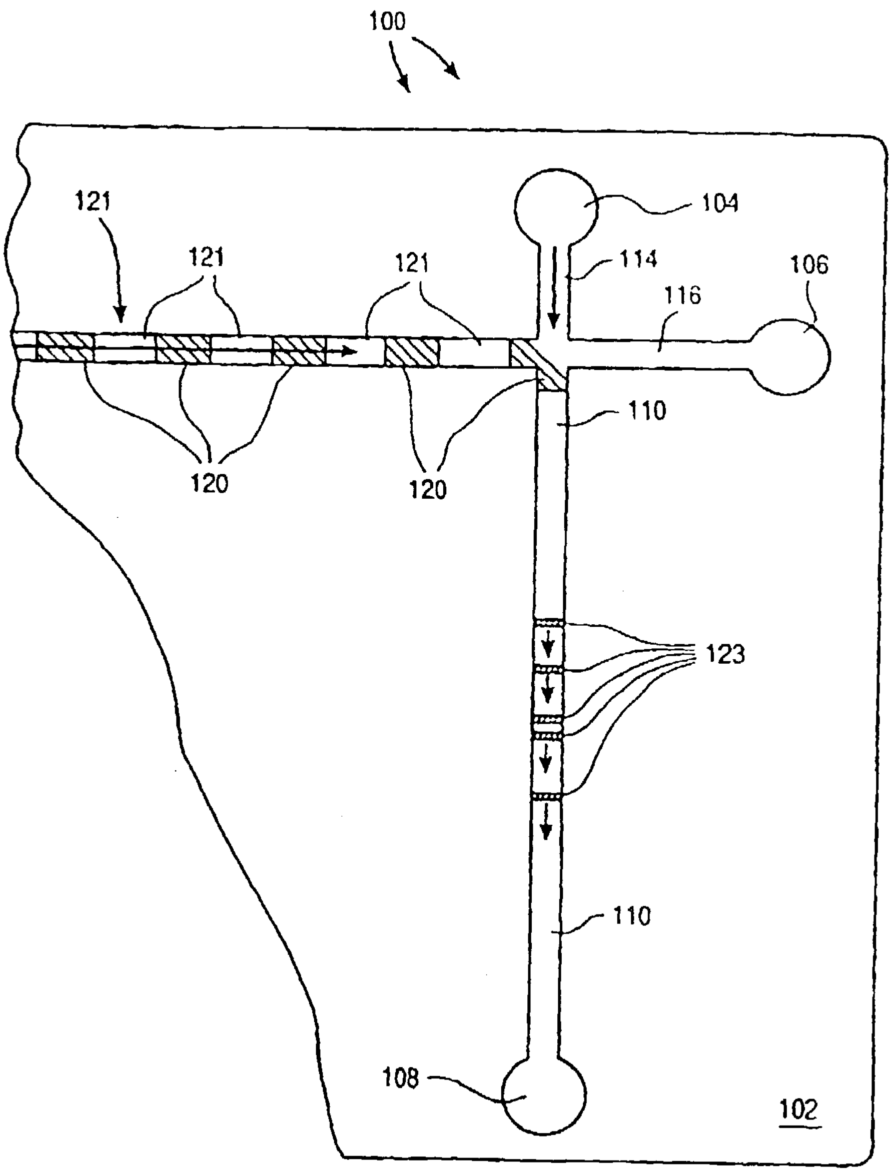

FIG. 1

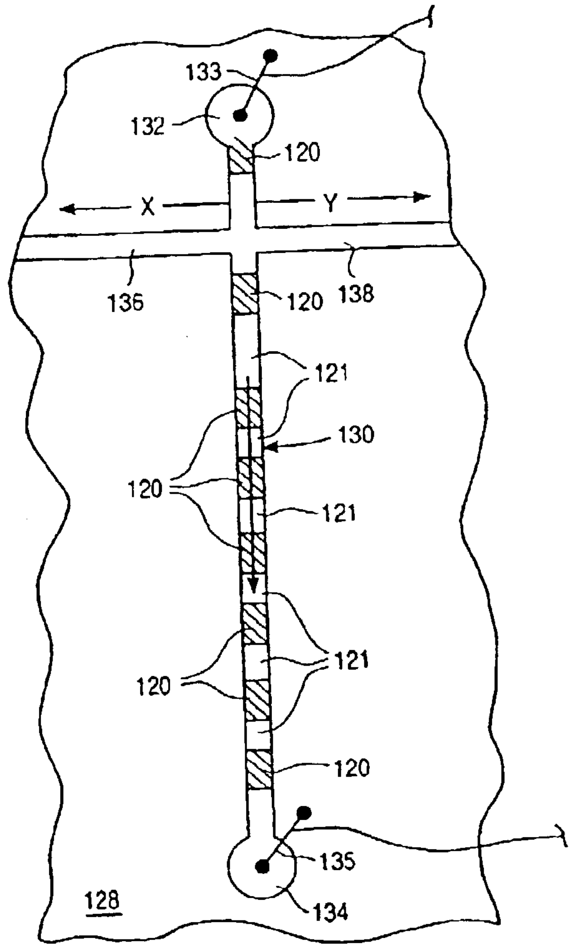
133
132
120
X
Y
136
138
120
121
130
120
121
120
121
120
135
128
134

FIG. 2A

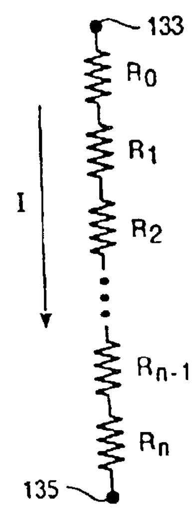
133
R_0
R_1
I
R_2
R_{n-1}
R_n
135

FIG. 2B

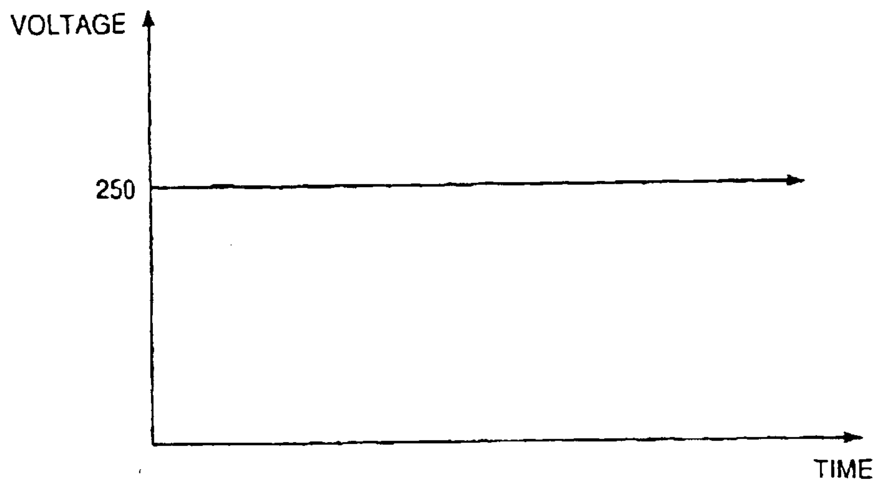

FIG. 3A (PRIOR ART)

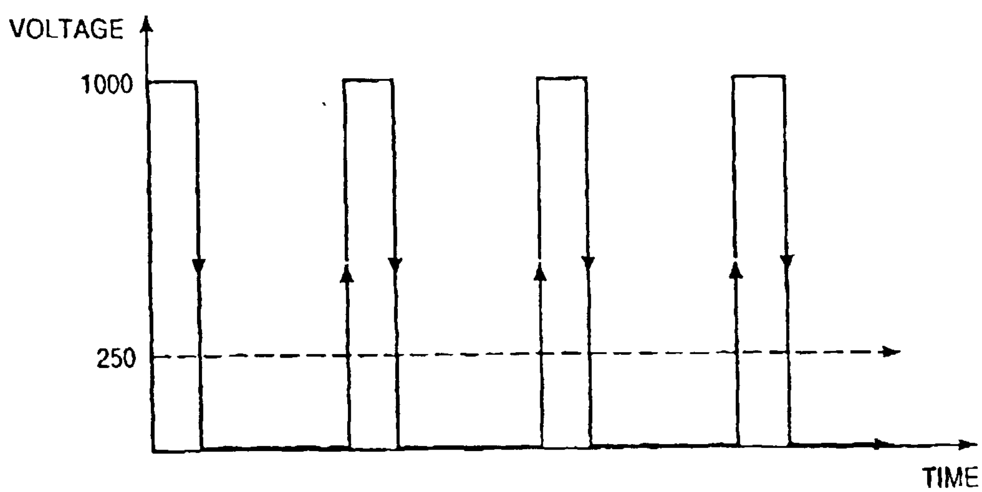

FIG. 3B

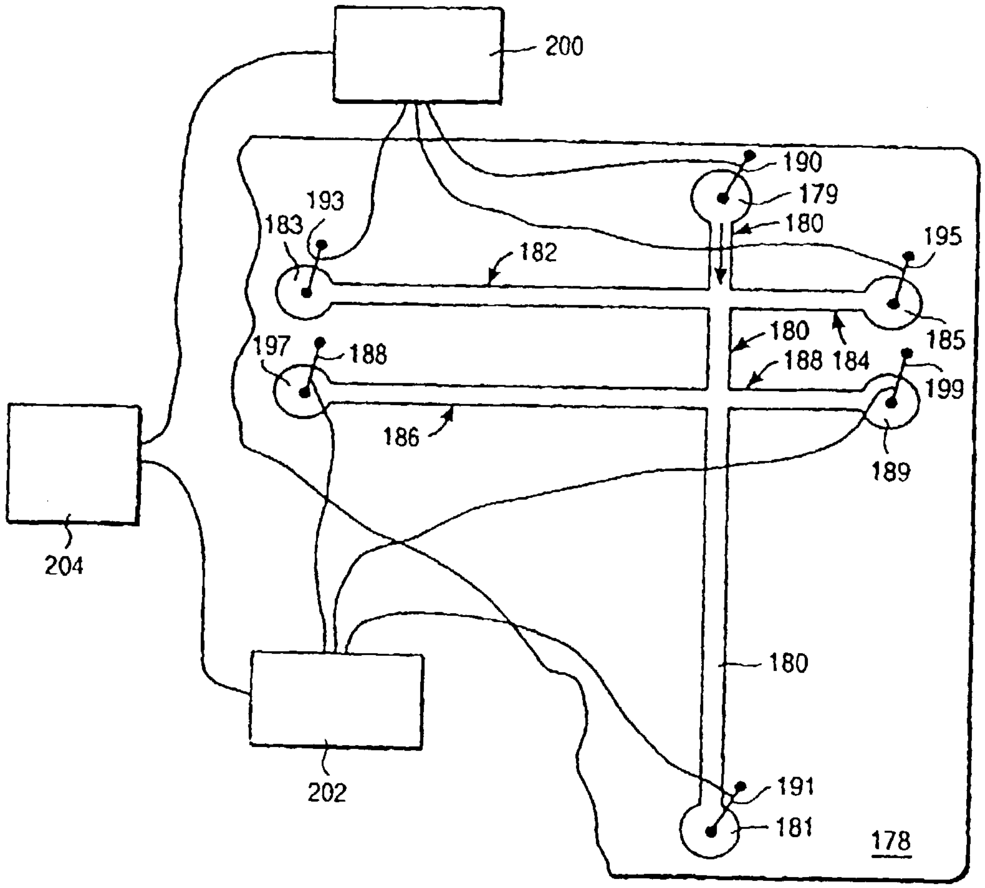
200
190
179
180
193
183
182
195
185
180
197
188
188 184
199
186
189
204
180
202
191
181
178

FIG. 4A

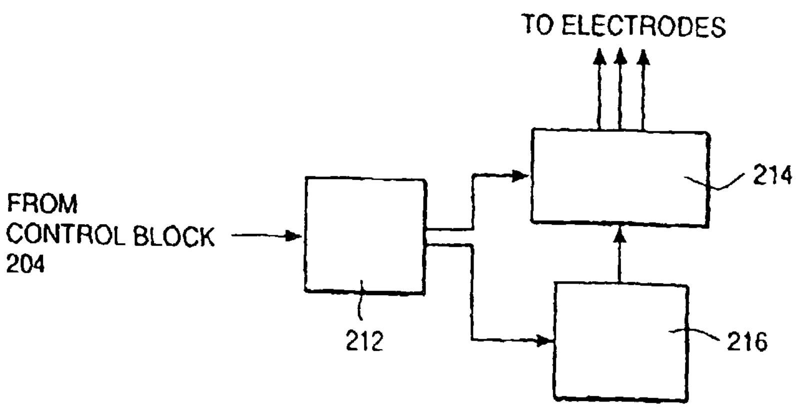
TO ELECTRODES
FROM
CONTROL BLOCK
204
214
212
216

FIG. 4B

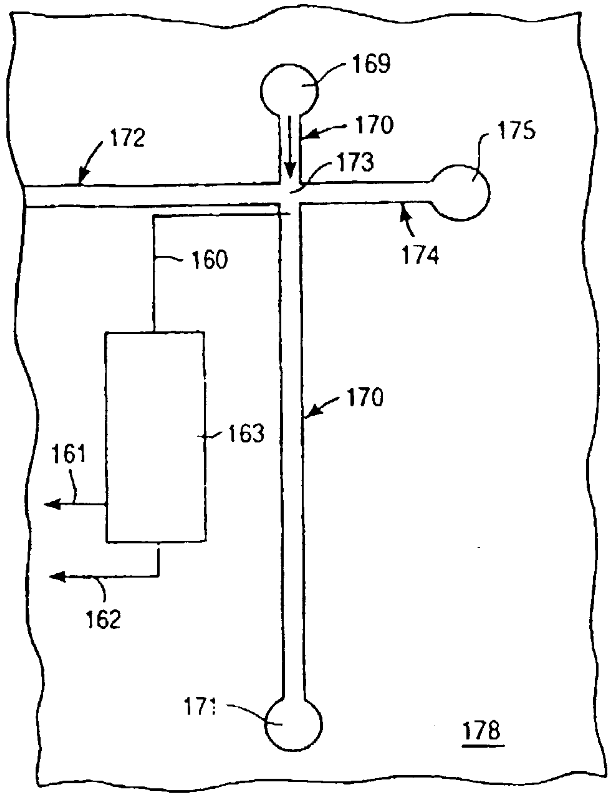
169
170
172
175
173
174
160
170
163
161
162
171
178

FIG. 5A

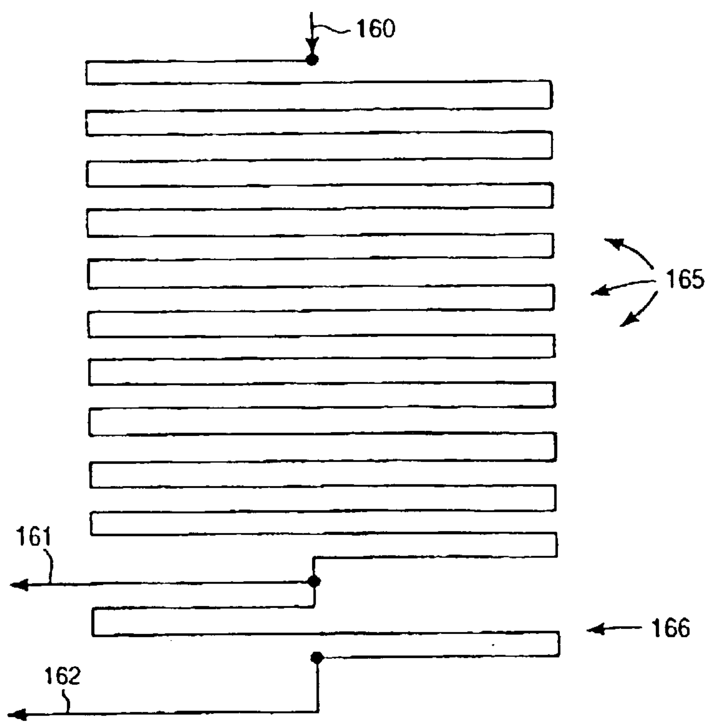
160
165
161
166
162

FIG. 5B

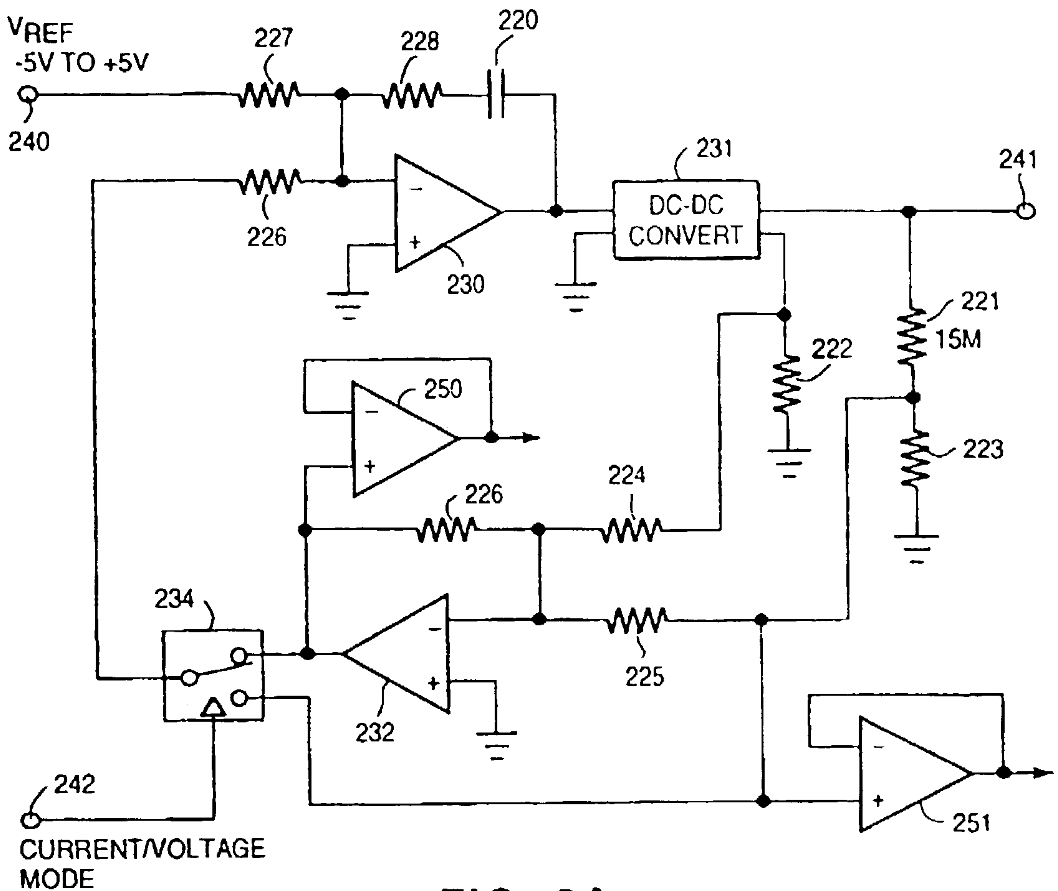
VREF
-5V TO +5V
240
227
228
220
226
230
231
DC-DC
CONVERT
241
221
15M
222
223
250
226
224
234
225
232
242
CURRENT/VOLTAGE
MODE
251

FIG. 6A

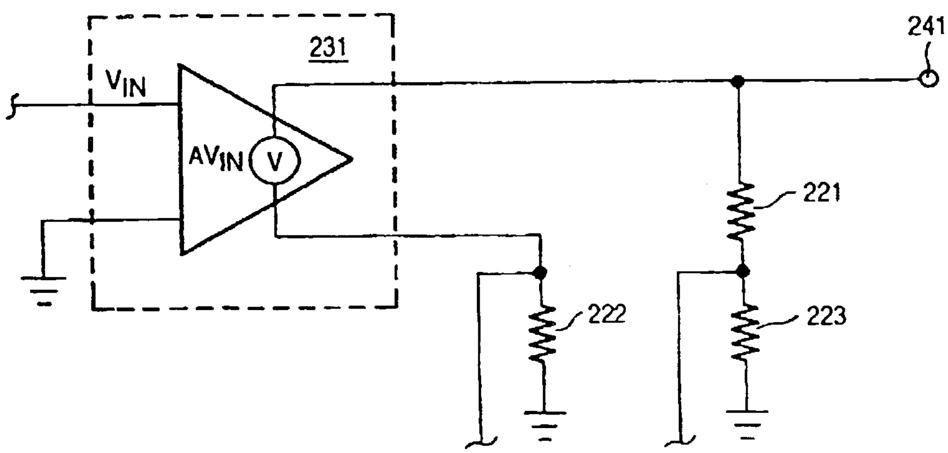
231
VIN
AVIN
V
241
221
222
223

FIG. 6B

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 30 4873

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	EP 0 070 963 A (SHIMADZU CORP.) * page 13, line 7 - page 14, line 20 *	1,4,32, 44	G01N27/447
Y	EP 0 544 969 A (CIBA-GEYGY) * column 7, line 25 - column 8, line 25 *	1,4,32, 44	
A	EP 0 365 321 A (EASTMAN KODAK CO.) * claim 1; figure 1 *	10,38,50	
A	EP 0 035 878 A (KUREHA KAGAKU KOGYO K. K.) * abstract; figure 1 *	10,38,50	
A	DE 24 12 956 A (PHARMACIA FINE CHEMICALS A.B.) * page 4, paragraph 1 - paragraph 2 *	15,24, 40,42	
A	DE 27 08 255 A (BISCHL) * page 3, paragraph 1; figure 1 *	31,43	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	EP 0 629 853 A (HEWLETT-PACKARD CO.) * abstract; figure 1 *	31,43	G01N
A	US 3 712 859 A (R. H. DILWORTH, III) * abstract * -----	32,34, 44,46	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	16 September 1997	Duchatellier, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document